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BARORECEPTOR REFLEX RESPONSE TO PHENYLEPHRINE AND CAROTID OCCLUSION IN MONKEYS RECEIVING 1000 RADS COBALT-60

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Nine conscious monkeys received phenylephrine and carotid occlusion tests of baroreflex function before and after 1000 rads Cobalt-60 exposure (dose rate = 170 rads/min). During the early postradiation minutes, concomitantly with hypotension and tachycardia, both baroreflex tests revealed depressed sensitivity (diminished blood pressure and heart rate changes). After 8-15 minutes postradiation, the phenylephrine, but not the occlusion

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test demonstrated a reversal to significant baroreceptor hypersensitivity which persisted 24 hours or more. No failure of the baroreflex mechanisms was suggested.

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PREFACE

This report presents findings on the effects of Cobalt-60 irradiation on the functional integrity of the baroreceptor reflex in monkeys. A previous study had concluded that the baroreflex mechanisms appeared to have suffered structural damage from irradiation, based on observations of diminished changes in blood pressure and heart rate in response to carotid artery occlusion following 1000 rads exposure or more.

The present experiment likewise observed diminished baroresponses during the first several minutes following 1000 rads, but it further showed that during the ensuing 20–60 minutes that a reversal to significant baroreceptor hypersensitivity comes about, which persists to some degree for one or more days. This later hypersensitivity was clearly demonstrated by the phenylephrine injection method, but could not be detected via the carotid occlusion tests. These findings consequently contradict the earlier report's suggestion of structural damage to the baroreflex system.

This experiment was part of a project studying the neurophysiological basis for primate performance decrement induced by radiation exposure. The work was conducted in accordance with the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," prepared by the National Academy of Sciences–National Research Council.

The authors gratefully acknowledge the assistance of A. N. Gallegos and R. G. Babb in the presentation of this work.

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BARORECEPTOR REFLEX RESPONSE TO PHENYLEPHRINE AND CAROTID OCCLUSION IN MONKEYS RECEIVING 1000 RADS COBALT-60

A. Bruner, A.W. Neely, E.A. Henderson, and G.K. Weiss

INTRODUCTION

In their attempt to understand the basis for radiation-induced hypotension in monkeys, Nathan and Craig[3] tested the baroreceptor reflex response to carotid occlusion in irradiated and control animals while under chloralose anesthesia. They reported that the initial response to carotid occlusion, which is an increase in blood pressure (BP) and heart rate (HR), was significantly diminished in the irradiated monkeys, and concluded that "postradiation damage to structures responsible for the maintenance of this reflex may have contributed to the rapid development of hypotension" (p. 554).[3]

Nathan and Craig's finding is important because it implies the presence of a radiation lesion within the nervous system structures mediating the baroreflex (e.g., brain stem and autonomic system), which, if true, would form the first anatomical target located for early postradiation hypotension and incapacitation. The present study attempted to replicate Nathan and Craig's finding but using phenylephrine injections[1] in addition to carotid occlusion for baroreflex testing. In addition, the present testing was done in unanesthetized monkeys.

METHODS AND MATERIALS

The subjects were nine male monkeys (Macaca mulatta), weighing between 3 and 4 kg. The animals were surgically implanted under halothane with femoral arterial and venous catheters, and subcutaneous ECG electrodes, one to six days prior to irradiation. Four of the monkeys were also implanted with hydraulic occluders* on the common carotid arteries. The arterial catheters were maintained patent by continuous infusion of heparinized saline (10 U/ml/15 mins) outside the experimental periods.

Arterial blood pressure within the abdominal aorta was monitored via the femoral catheter with a Kulite PSL 125-6 Pressure Transducer** and a polygraph write-out. Phenylephrine injections (40–160 μg) were introduced via the femoral vein catheter by a remotely operated pump.***

The animals received 1000 rads, mid-body dose, of Cobalt-60 gamma at the Air Force Weapons Laboratory Large Animal Irradiation Facility, located on Kirtland AFB, Albuquerque, New Mexico. Each animal was restrained in a plastic chair and oriented with its back toward the Co^{60} source at a distance producing a mid-body dose rate

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* Rhodes Medical Instr. Model VO-3, 2mm. 21044 Ventura Blvd., Woodland Hills, Calif. 91364.

** Kulite Semiconductor Products, 1039 Hoyt Ave., Ridgefield, New Jersey, 07657.

*** Filamatic Vial Filler, Model AB. National Instrument Co., Baltimore, Md.

of approximately 170 rads/min (duration = 5.9 minutes). Further details of the exposure parameters and dosimetry are available in Ref. 2.

Baroreflex Tests

Figure 1 (right) depicts a polygraph record of a typical response to rapid phenylephrine injection, where BP rises due to the vasoconstrictive action of the drug, while HR drops as a manifestation of the baroreceptor reflex to the increased pressure. This effect is transient and the injections may be repeated within minutes without cumulative effects. Sensitivity of the baroreceptor response may be expressed by plotting systolic BP against the interbeat interval (in msec or inverted to HR) which starts with the R-wave following the BP determination, for every beat occurring during the approximately 10-second observation period starting 2 seconds after the injection and ending at the peak pressure.* The slope of the linear regression fit to these data points reflects the baroreflex sensitivity at that time.[4]

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* In humans, the first R-R interval following the BP measurement reportedly yields the highest HR-BP correlation coefficients.[4] In the monkey, where the R-R interval may be only one-third as long as in man, allowing less time for the reflex to act, we found that the second R-R interval following the pressure reference yields the higher correlations.

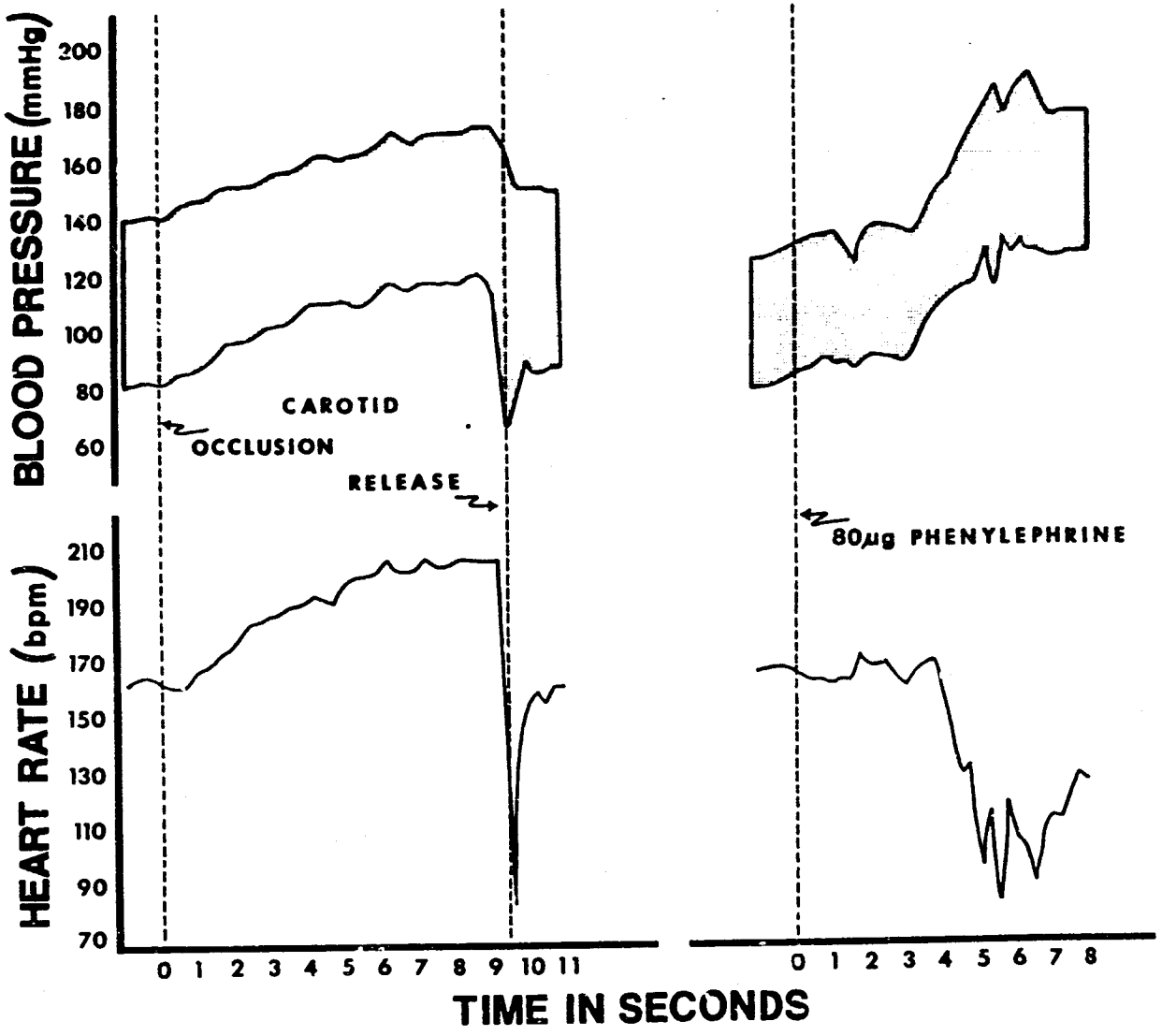

Figure 1. Polygraph displays of BP and HR responses to double carotid occlusion (left) and intravenous phenylephrine injection (right).

Phenylephrine was injected just prior to irradiation and at frequent intervals during the first hour postradiation, and again 24 or more hours later. The BP and HR responses to these injections constitute the chief body of data for this report.

Figure 1 (left) shows the effects of occlusion of the carotid arteries. On occlusion, the baroreceptors sense low pressure and bring about compensatory increases in both arterial BP and HR. Opposite responses in BP and HR are seen when the occluders are released. The four monkeys carrying occluders received 10-second occlusion tests just prior to each pre- and postradiation phenylephrine injection. Three of the four subjects each had two occluders, one on each common carotid artery. In these cases, both single and double carotid occlusion tests were performed. The fourth monkey (No. 717) had only one patent carotid artery as the other one was damaged during pretesting.

Figure 2 presents examples of how the phenylephrine baroreflex curves may undergo change and how the changes are measured. Two types of change and their combination are considered in the present situation. First, the slope (sensitivity) may be altered. Second, the relation (set level) between BP and HR may change (e.g., slower or faster HR for a given BP). Or both slope and set level may change due to the experimental manipulations.

Figure 2-I shows a shift to higher sensitivity (steeper slope) from line A to B and to a lower sensitivity from A to C. At the reference systolic BP of 150 where the three lines cross, the same HR of 200 bpm is observed, which means that no resetting of the reflex has occurred

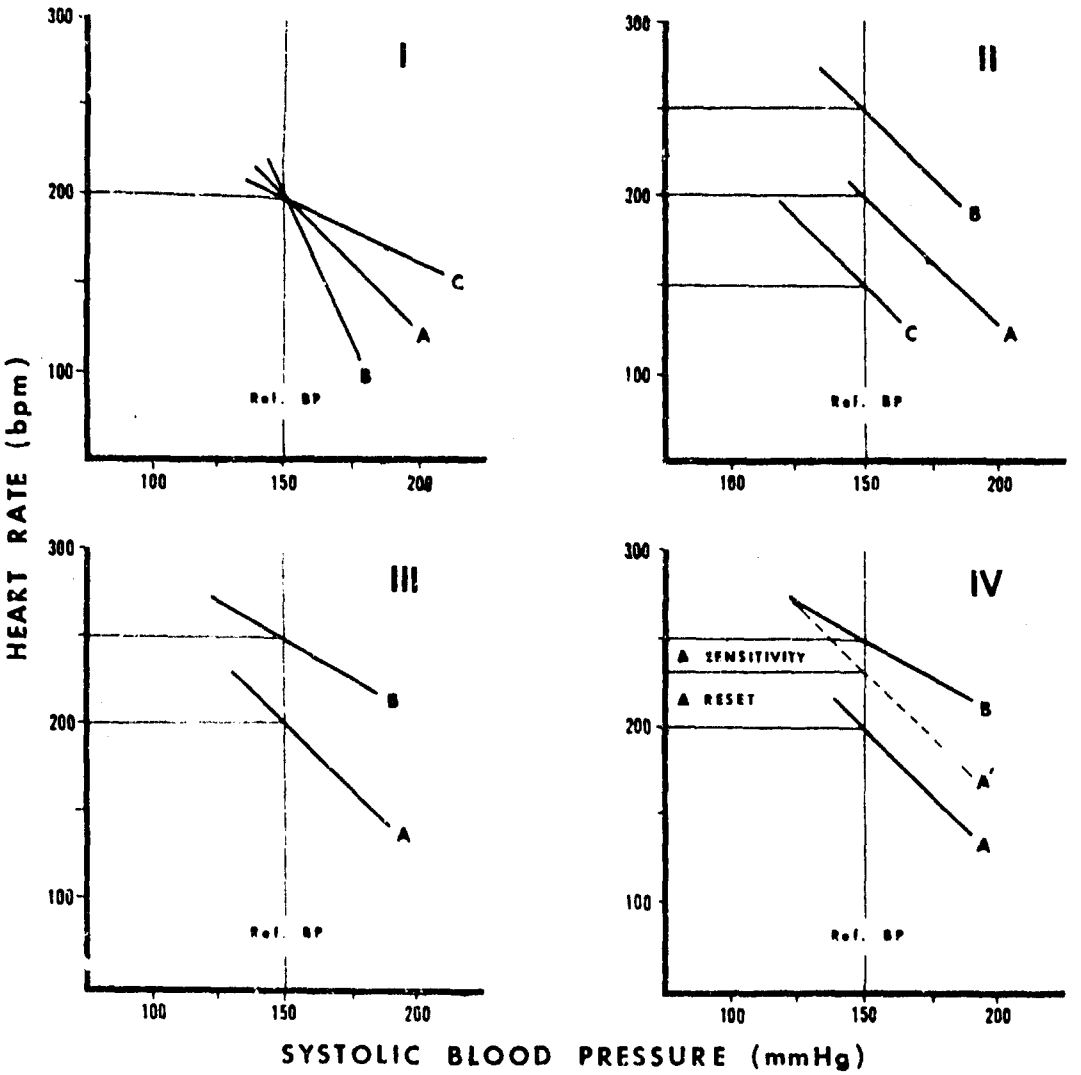

Figure 2. Examples of shifts in sensitivity (I), set level (II), both (III), and the layout arrangement (IV) for determining the amount of change (Δ) in each, expressed in bpm, after Bristow, et. al.[1]

(same $HR|BP_{150}$). In Figure 2-II, the BP-HR relation is shown resetting to a faster (A to B) and a slower HR (A to C) given the reference BP of 150 mm Hg, without altering the slope (sensitivity). Figure 2-III shows a combination of changes in sensitivity and set level.

Figure 2-IV shows how the relative changes in set level and sensitivity shown in Figure 2-III would be measured according to the method of Bristow et al.[1] The line of slope A, which would be the preradiation curve in the present case, is redrawn (A') at the origin of slope B, the postradiation regression line. The distance between the original (A) and transposed (A') preradiation slopes at an arbitrary BP reference (150 mm Hg), is taken as the amount of resetting, expressed here in beats per minute (bpm). The distance in bpm between the postradiation slope B and the transposed preradiation line (A') at the reference BP reflects the shift in sensitivity.

The dose of phenylephrine was adjusted to give a clear increase in BP where possible. Before radiation the adequate dose ranged from 40–80 μg (in 0.2–0.4 ml, within 1–2 seconds). Immediately following radiation, 80–160 μg was necessary due to a diminished vasoconstrictive response at that time. Twenty minutes postradiation 40–80 μg was again sufficient. The actual dose is unimportant, so long as it is enough to produce an adequate pressure rise for the purpose of sensitivity measurements, because the slope of the resulting regression line is not affected by dose, only the length of the line is affected which is simply the extent of the BP change.

RESULTS

Phenylephrine Tests

Figure 3-A displays the baroreflex responses to phenylephrine pre- and postradiation for a representative monkey (No. 745). At the origin (left end) of the 4-minute postradiation curve, the high HR and low BP typical of the early postradiation minutes is evident. Relative to preradiation, the 4-minute curve indicates a very depressed sensitivity (flattened slope) in response to the phenylephrine injection. Here the HR changes only very slightly as the BP is raised. Additionally, the vertical displacement of the 4-minute curve relative to that for preradiation indicates that the reflex has been reset slightly to a new level, such that for the same reference BP, the HR is slightly slower.

The 11- and 28-minute postradiation slopes in Figure 3 reveal a dramatic reversal from the initial postradiation depression to a condition of hypersensitivity. Furthermore, the heightened sensitivity is maintained on the following day.

Figure 3-B (left) presents plots over time of the slope constants calculated for the baroreflex regression lines shown in Figure 3-A. Figure 3-B includes some additional data points not plotted in 3-A for clarity. This graphical presentation of the slope constants also depicts the initial hyposensitivity of the reflex followed by hypersensitivity. All nine monkeys revealed baroreflex hyposensitivity at some time during the initial 10 minutes following raising the Cobalt-60 source.

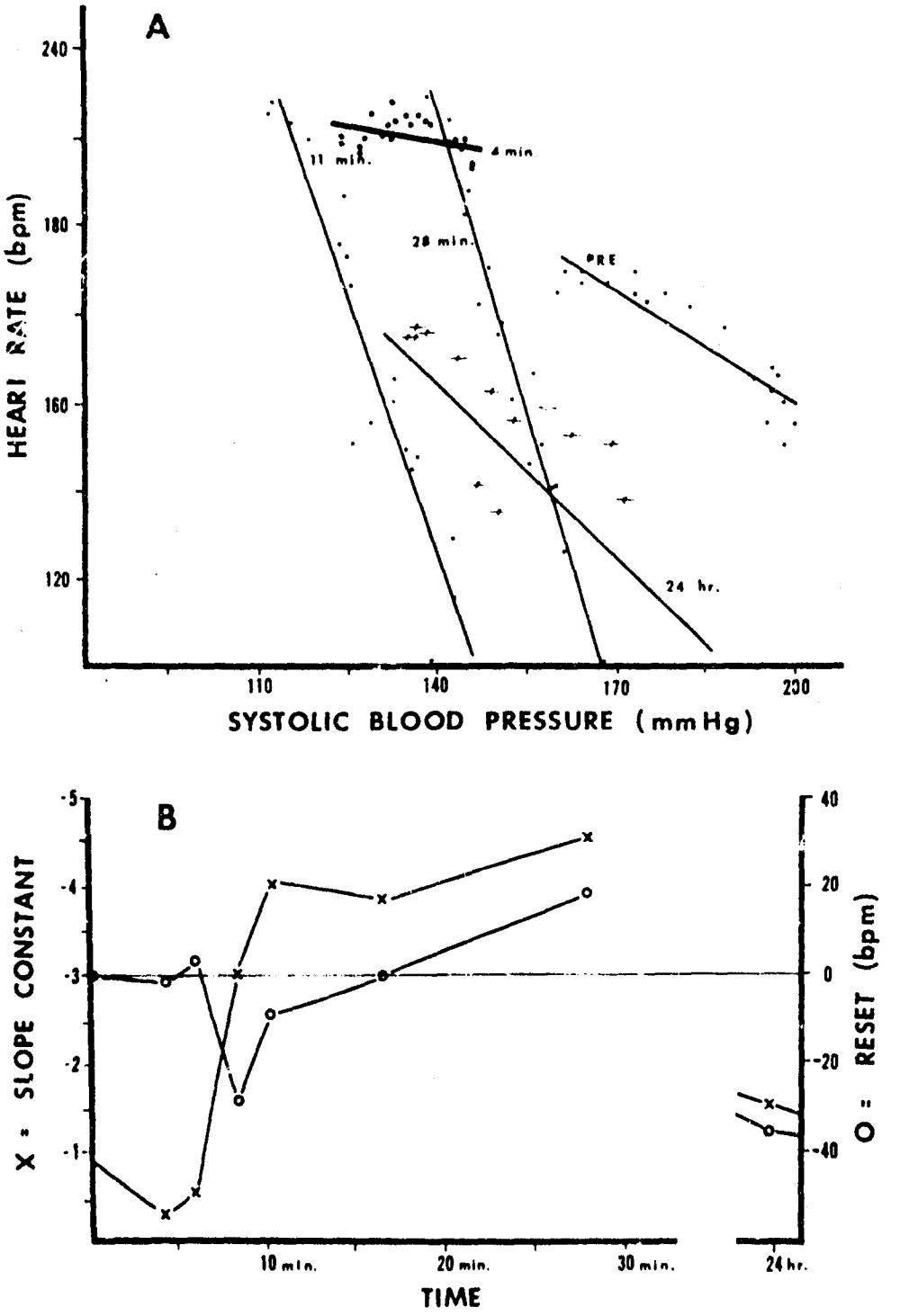

Figure 3-A. HR-BP data points and linear regression lines for Monkey #745's responses to phenylephrine injections preradiation and at 4, 11, 28 minutes and 24 hours postradiation.

3-B. (left): Plot of slope constants for each of #745's phenylephrine tests. Relative to the preradiation value (-.87), the 4 and 6-minute values reflect flatter slopes (baroreflex hyposensitivity), while hypersensitivity is indicated by the larger negative slope constants later.

3-B. (right): Plot of reset shifts calculated as in Figure 2, for each of #745's postradiation phenylephrine tests.

For six of the animals the depressed sensitivity was significantly different from the preradiation sensitivity (t-tests for difference between slopes, $p<.05$)

Eight of the nine animals showed significantly hypersensitive baroresponses (steeper slopes) to phenylephrine for one or more of the injections administered between 20 and 70 minutes following source-up, relative to preradiation. The peak hypersensitivity varied from 25 to 60 minutes for all but one subject whose peak occurred at 24 hours. All animals tested maintained some reflex hypersensitivity at the 24-hour postradiation observations. Figure 3-B (right hand ordinate) also presents for Monkey No. 745 a plot of the reset shifts calculated as in Figure 2-IV. The resets are small and tend to be toward slower HR's initially postradiation. At 28 minutes, however, there is a faster $HR|BP_{150}$ set level. At 24 hours the reset indicates a slower HR for the reference BP.

Eight of the animals showed a resetting to a lower $HR|BP_{150}$ during the first 8 minutes following source-up. During the ensuing hour, however, the direction of the reset shift was variable. By 24 hours postradiation, the same eight animals had resumed the slower $HR|BP_{150}$ set level.

As all of the animals' baroreflex curves revealed shifts in both sensitivity and set level, the respective contribution of each was examined by the method of Bristow *et al.*,[1] described earlier (Fig. 2-IV). These results are presented in Table I for each subject for each postradiation phenylephrine test compared to that from preradiation. The

postradiation trends described earlier are reiterated in Table I. Generally there is a negative sensitivity shift up to 8–15 minutes postradiation, followed by a positive shift for all but one animal, peaking between 30 and 60 minutes. The positive sensitivity changes are still maintained after 24 hours.

During the initial 15 minutes postradiation, again the trend apparent in Table I is toward a resetting of the reflex to a slower $HR|BP_{150}$. During the period from 15–60 minutes, the animals are about equally divided in showing positive and negative resets, while all but one showed hypersensitivity at this time. At 24 hours, all but one subject showed a decreased $HR|BP_{150}$ (negative reset).

Second Irradiations

Three animals (Nos. 730, 725, and 735) received second 1000-rad exposures 24 hours following the first irradiation. For the purpose of evaluating sensitivity and set level shifts, the 24-hour postradiation phenylephrine regression line was employed as the preradiation line for the second postradiation slope comparisons. Two of the animals, 730 and 735, revealed similar shifts in both resetting and sensitivity as compared to their first irradiation. The third monkey showed opposite shifts in both measures following the second irradiation.

Occlusion Tests

Table II presents the results of the carotid occlusion tests before and after irradiation on the four animals so implanted. The

Table I Postradiation Shifts in Baroreflex Set Level and Sensitivity

Monkey		Minutes Postradiation																				Hours Postradiation		
		4	6	7	8	9	10	11	12	13	15	16	17	18	20	25	30	40	45	50	60	75	4	5	24	
745	R	-2	4		-27			-7					0				18								-3	-31
	S	18	-12		102			115					50				39								14	10
730	R	-31		-19			-25				-44				-53		-96	-130				-128				-60
	S	10		-2			1				3				4		16	60				77				-3
776	R				-10							71				51		35				17		-16	-31	
	S				-4							-4				21		28				43		3	10	
726	R		44						37							37		38				37	42		43	
	S		-23						-9							16		25				15	17		19	
743	R					-36						15				14		-6			-1	17			-29	
	S					-109						56				100		161			288	122			42	
729	R				-40					-16				-40			-44				-61	-47		-27	-64	
	S				-11					8				7			-19				39	38		39	73	
725	R			-89				-41					-78		-126			-87	-103			-120			-130	
	S			-40				-13					-6		-12			-1	-8			-10			0	
735	R								-161					-53				-134			-141				-76	
	S								-68					19				89			37				66	
717	R				-2						86					66	60		51			94			-4	
	S				-145						-36					112	88		84			80			40	

Note: A positive R value indicates a reset to a higher $HR|BP_{150}$. A negative R indicates a reduced $HR|BP_{150}$. The preceding is opposite to the convention adopted by Bristow, et al.[1] Positive and negative S values respectively indicate increased and decreased sensitivity. All values are expressed in bpm.

Table II Postradiation Changes in HR and BP Associated With Carotid Occlusion

				Minutes Postradiation															
		Preradiation		8		15		25		35		40		48		62		24 Hours	
Monkey	Occlusion	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP	HR	BP
	During	180	165	231	112	226	173	213	144			132	184			232	154	225	144
726	Before	167	146	235	103	211	133	203	136			106	127			215	123	221	118
	Diff	13	19	-4	9	15	40	10	8			26	57			17	31	4	26
	During	190	211	258	122	249	153	228	153			232	164			219	149	176	155
776	Before	150	174	259	119	244	137	200	141			219	132			200	127	160	129
	Diff	40	37	-1	3	5	16	28	12			13	32			19	22	16	26
	During	215	198	254	62	240	122	235	133	237	106			235	102	252	122	199	236
743	Before	158	143	257	49	240	104	226	111	235	98			230	88	245	102	172	114
	Diff	57	55	-3	13	0	18	9	22	2	8			5	14	7	20	27	22
	During	175	147	278	67	290	103	279	114	257	130			261	124	271	112		
717	Before	158	134	280	55	290	86	280	99	245	115			240	113	260	101		
	Diff	17	13	-2	12	0	17	-1	15	12	15			21	11	11	11		

data for animals 726, 776, and 743 represent the changes in HR and BP following simultaneous occlusion of both common carotid arteries. Single occlusions were also performed, but those data are not given here as they did not differ from the double occlusion data except in being of smaller magnitude. Animal 717 had only one intact carotid artery so that its single occlusion data likewise reflect complete carotid flow stoppage.

In Table II, the "before" values of HR and BP are the averages of the five beats immediately preceding each occlusion test. The "during" values are the averages of five beats taken from 6 to 10 seconds following the occlusion's onset. Each occlusion was held about 10 seconds. The differences between each "before" and "during" occlusion value for HR and BP indicate the changes in baroreflex responsiveness when viewed over time postradiation.

The depression of baroreceptor function is evident from the occlusion difference scores during the first 15 minutes postradiation in Table II. Recovery to somewhat lower than normal values occurs during the subsequent 45-minute test period and remains unchanged the next day. Only Monkey 726 revealed a tendency toward reflex hypersensitivity at 15 and 40 minutes and thereafter, based on the occlusion difference scores.

The occlusion findings are therefore consistent with the phenylephrine tests run on these four monkeys in demonstrating an initial postradiation depression of the baroreflex. But the occlusion data fail to reveal clearly the hyperreflexia which appeared in the later postradiation

minutes for these four monkeys, and that which also appeared in three of the remaining four monkeys not carrying occluders when tested with the phenylephrine method.

DISCUSSION

Nathan and Craig[3] made single determinations of the baroreflex response to carotid occlusion shortly after each of ten, 1000-rad exposures. The duration of their X-ray exposure ranged from 5.9 to 8.0 minutes (average dose rate of 158 rads/min). Each exposure was followed by a 5 minute period during which the occlusion test was performed, following which the next exposure was given. This sequence was repeated for a total of 10 irradiations. They observed diminished HR and BP rises to carotid occlusion for the majority of the 10 tests.

The postradiation occlusion test performed by Nathan and Craig following their first irradiation, corresponds in time to our own initial postradiation occlusion and phenylephrine tests under similar exposure conditions. We also observed depressed HR and BP responses to occlusion, and depressed phenylephrine sensitivities during the first several minutes postradiation. But in the next 10 minutes or so, our observations revealed that the phenylephrine reflex rapidly became hypersensitive, reaching peak hypersensitivity between 30 and 60 minutes postradiation. Some heightened sensitivity was apparent 24 hours later at which time a second 1000 rads tended to bring about the same cycle of hyposensitivity followed by hypersensitivity as had occurred after the first irradiation. Nathan and Craig could not have seen the later hypersensitivity because

only 5 minutes of postradiation testing was done before the subsequent exposure, and because the subsequent exposure could be expected to further depress the reflex.

Our own occlusion tests, in four animals also tested with phenylephrine, demonstrate that the occlusion method does not show the development of postradiation baroreflex hypersensitivity shown by the phenylephrine method. Thus, even if Nathan and Craig had not reirradiated their animals and had allowed longer postradiation test periods, they still might not have seen a later developing hypersensitivity due to the apparent shortcomings of the occlusion method.

While demonstrating postradiation alterations in the sensitivity and set level of the baroreflex system, the present results indicate that it is most unlikely that structural damage, in the sense of an anatomical lesion, could have occurred to the system in view of the consistent hyperreflexive responses to phenylephrine within 20 minutes of irradiation. Furthermore, the baroreflexes were not only functional but still hypersensitive 24 hours after irradiation at which time a second 1000 rads could produce effects similar to the first.

Many investigators have observed that a new resting BP level, somewhat lower than before irradiation, becomes established and is maintained after about 20 minutes postirradiation within the present dose range. Our animals, quite uniformly, showed a downward resetting of HR in conjunction with this lowered BP. In addition, a new, more sensitive baroreflex response developed at this time. These changes would appear to be an adaptive response by the baroreflex control

center such that a roughly normal HR was set to a chronically low BP, while an increased baroreflex sensitivity attempted to meet cardiac output demands with supernormal changes in HR in response to relatively small changes in pressure. This sort of adaptive plasticity implies a highly functional neural control mechanism, not one damaged by radiation.

Thus, while we would reject the notion of structural damage to the baroreflex system, we would not disagree with the proposition that the system, on becoming initially hyposensitive to pressure changes following irradiation, may contribute passively to the development of early hypotension by failing to mediate compensatory pressure increases.

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